01-18-07

PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Most, *et al.*

Appl. No.: 10/572,416
(National Stage of PCT/EP2004/009621)
Filed: March 16, 2006

For: **Process for the Production of Alpha-Alkoxy/ Hydroxy-Beta-(P-Hydroxyphenyl) Propionic Acid Derivatives**

Confirmation No.: none

Art Unit: to be assigned

Examiner: to be assigned

Atty. Dkt.: 7601/88086

Petition under 37 C.F.R. § 1.181 to Accord Filing Date (Original Application Papers Lost by U.S.P.T.O.)

MAIL STOP Petitions
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.181, Applicants hereby petition for the enclosed papers to be accepted as the National Stage of PCT/EP2004/009621 and accorded a filing date of March 16, 2006. The enclosed papers, which comprise a complete copy of the undersigned's file, were originally filed on that date, but no filing receipt has been received and, after conversations with U.S.P.T.O. officials, it appears likely that the application papers have been misplaced or lost by the U.S.P.T.O.

I. Background and Proof of Filing

The enclosed papers were timely filed on March 16, 2006. The filing itself included a nine-page specification, two pages of claims, a one-page abstract, signed declarations from the inventors (executed at the time of filing the PCT Request in the International Phase), copies of papers concerning the PCT application, and other transmittal papers. At the time the papers were filed, standard procedure at the Fitch, Even, Tabin & Flannery law firm, which handled the filing, was to transmit the papers to the U.S.P.T.O. by messenger with two postcards: the first postcard would be stamped by the Office of Initial Patent Examination at

the customer service window and returned to the firm by the messenger, and the second postcard would be returned by mail by the U.S.P.T.O. once an application number was assigned. To the best of the undersigned's knowledge, that procedure was followed in this case.

Enclosed with this petition are copies of both postcards. The first postcard clearly bears an OIPE stamp from March 16, 2006; the second postcard is stamped by the PCT branch with the date of March 16, 2006 and the application number 10/572,416. The undersigned notes that the contents of the filing were clearly enumerated on both postcards, and that neither postcard contains any annotation indicating that the described contents were not received. Therefore, pursuant to the guidelines in MPEP § 503, the postcard receipts are *prima facie* evidence that the application was filed. The undersigned also notes that the filing fees were authorized to be charged to Deposit Account No. 06-1135; however, to the best of the undersigned's knowledge, that Deposit Account was never charged for the filing fees.

II. Present Status of the Application

On January 12, 2007, after being unable to find any record of the application in the Private PAIR system, the undersigned contacted the U.S.P.T.O.'s Electronic Business Center, followed by calls to the Office of Initial Patent Examination and the PCT Branch (via the PCT Helpdesk). After discussions with officials from all three entities, it became clear that the U.S.P.T.O. had no record of this application having been filed.

III. This Petition

The enclosed papers represent a complete copy of all correspondence with the U.S.P.T.O. relating to this patent application. The undersigned is not aware of any correspondence that is not enclosed with this petition. Given the nature of this petition, no fee is believed to be due; however, if that is incorrect and a fee is due, the fee may be charged to Deposit Account No. 06-1135, under our order no. 7601/88086.

Applicants hereby ratify any statements or authorizations that were made in the enclosed papers, to the extent that ratification might be necessary. In particular, the filing fees may be charged to Deposit Account No. 06-1135, as was originally authorized.

However, the correspondence address for this application has changed; therefore, please see the attached change of correspondence address.

In view of the foregoing, Applicants respectfully request that this petition be treated quickly and favorably. If any questions arise, or any elements necessary to decide the petition are missing, the undersigned would appreciate a telephone call so that those issues can be addressed with alacrity.

Respectfully submitted,

Law Office of Michael A. Sanzo, LLC

By Andrew McAleavey
Andrew McAleavey
Reg. No. 50,535

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date January 17, 2007
Customer No. 66991
15400 Calhoun Drive, Suite 125
Rockville, Md. 20855
Phone: (240)864-0915
Fax: (240)597-1153
E-mail: mike@msanzolaw.com

Enclosures:
National Stage of PCT/EP2004/009621, as filed on March 16, 2006 with 2 proof of filing postcards.
Change of correspondence address

Certificate of Mailing by Express Mail

The undersigned hereby certifies that this document and its described enclosures were mailed on January 17, 2007 by Express Mail Post Office to Addressee label no. EQ788231235US, addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 with sufficient postage.

Andrew McAleavey
Andrew McAleavey

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Most, *et al.*

Appl. No.: 10/572,416
(National Stage of PCT/EP2004/009621)
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Examiner: to be assigned

Atty. Dkt.: 7601/88086

Change of Correspondence Address

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Please associate the above-identified patent application with **customer number 66991** and direct all future correspondence in this application to the address associated with **customer number 66991**.

Respectfully submitted,

Law Office of Michael A. Sanzo, LLC

By Andrew McAleavey
Andrew McAleavey
Reg. No. 50,535

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date January 17, 2007

Customer No. 66991
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Rockville, Md. 20855
Phone: (240)864-0915
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E-mail: mike@msanzolaw.com

RECEIPT FROM USPTO FOR INDICATED ITEMS

Appln. No.:	TO BE ASSIGNED	Attorney:	M. Sanzo
Filed:	HEREWITH	Date:	March 16, 2006
Inventor(s):	MOST, *et al.*	Atty. Dkt.:	7601/88086
Title:	**PROCESS FOR THE PRODUCTION OF α-ALKOXY/HYDROXY-β-(p-HYDROXYPHENYL) PROPIONIC ACID DERIVATIVES**		

WHEN RECEIPT STAMP IS PLACED HEREON, THE USPTO ACKNOWLEDGES RECEIPT OF THE FOLLOWING DOCUMENTS; OUR COVER LETTER ENCLOSING:

1. Application Data Sheet;
2. A copy of PCT/EP2004/009621 as filed on August 26, 2004, and naming as inventor(s): Dieter Most, pavol Jakubec and Kai Rossen
   the application comprising: 9 pages of Specification (numbered as pages 1-9),
   2 pages of Claims (numbered as pages 19-11), and a one-page Abstract (numbered as page 12);
3. Preliminary Amendment;
4. A copy of the PCT Request with a copy of Declarations executed by the inventors attached;
5. A copy of the PCT application, as published;
6. A copy of the International Search Report;
7. A copy of the Written Opinion of the International Searching Authority;
8. General Authorization for Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(3);
9. General Authorization to Charge Deposit Account;
10. A copy of PCT/IB/304, Notification Concerning Submission or Transmittal of the Priority Document;
11. A copy of PCT/IB/308 Notice Informing the Applicant of the Communication of the International Application to the Designated Offices;
12. A copy of PCT/IB/371, Notification Relating to Declaration made under PCT Rule 4.17, confirming the receipt of the Declaration of Inventorship within the time limit under PCT rule 26ter; and
13. Two (2) return postcards.

Fees totaling $ 1,260.00 to be charged to Deposit Account No. 06-1135.

PLEASE DATE STAMP AND RETURN BY COURIER
FITCH, EVEN, TABIN & FLANNERY

RECEIPT FROM USPTO FOR INDICATED ITEMS

Appln. No.:	TO BE ASSIGNED	Attorney:	M. Sanzo
Filed:	HEREWITH	Date:	March 16, 2006
Inventor(s):	MOST, *et al.*	Atty. Dkt.:	7601/88086
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1. Application Data Sheet;
2. A copy of PCT/EP2004/009621 as filed on August 28, 2004, and naming as inventor(s): Dieter Most, pavol Jakubec and Kai Rossen
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   2 pages of Claims (numbered as pages 19-11), and a one-page Abstract (numbered as page 12);
3. Preliminary Amendment;
4. A copy of the PCT Request with a copy of Declarations executed by the inventors attached;
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6. A copy of the International Search Report;
7. A copy of the Written Opinion of the International Searching Authority;
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Fees totaling $ 1,260.00 to be charged to Deposit Account No. 06-1135.

PLEASE HOLD FOR SERIAL NUMBER

Billing Confirmation

Thank you for submitting your request for payment. This page is your official receipt and should be printed and included with copies of your filing papers as part of your physical file record.

Here is the information we have recorded:

Date of Transaction: 3/16/2006
Requesting Attorney: 6126
Requesting User: ctavernese
Client Number: 7601
Matter Number: 88086
Application Number: Not Yet Assigned
Country: US
PTO Code(s):

Transaction Number: 28170 Basic National Stage Fee	$300
Transaction Number: 28171 National Stage Search Fee - search report prepared and provided to USPTO	$400
Transaction Number: 28172 National Stage Examination Fee	$200
Transaction Number: 28173 Claims - multiple dependent	$360
Total Amount:	$1260

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FITCH, EVEN, TABIN & FLANNERY

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March 16, 2006

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*ADMITTED TO D.C. BAR
D.C. PRACTICE OF ALL OTHERS
LIMITED TO FEDERAL COURTS
AND AGENCIES

Commissioner of Patents
U.S. Patent and Trademark Office
Customer Service Window, **MS PCT**
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Re: Entry into National Stage for:

Intl. Appl. No.:	PCT/EP2004/009621
Intl. Filing Date:	August 28, 2004
For:	**Process for the Production of α-alkoxy/ hydroxy-β-(p-hydroxyphenyl) Propionic Acid Derivatives**
Inventor(s):	Most, *et al.*
Atty. Dkt.:	7601/88086

Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Application Data Sheet;

2. A copy of PCT/EP2004/009621 as filed on August 28, 2004, and naming as inventor(s):

Dieter Most
Pavol Jakubec
Kai Rossen

the application comprising:

9 pages of Specification (numbered as pages 1-9),
2 pages of Claims (numbered as pages 19-11), and
a one-page Abstract (numbered as page 12);

3. Preliminary Amendment;

4. A copy of the PCT Request with a copy of Declarations executed by the inventors attached;

5. A copy of the PCT application, as published;

6. A copy of the International Search Report;

7. A copy of the Written Opinion of the International Searching Authority;

8. General Authorization for Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(3);

9. General Authorization to Charge Deposit Account;

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12. A copy of PCT/IB/371, Notification Relating to Declaration made under PCT Rule 4.17, confirming the receipt of the Declaration of Inventorship within the time limit under PCT rule 26ter; and

13. Two (2) return postcards.

This application represents U.S. national stage of international application PCT/EP2004/009621, which had an international filing date of August 28, 2004. The international application claims priority to German application 103 43 097.0, filed on September 18, 2003. The present application claims priority to these previously filed counterparts and incorporates them by reference.

The Director is hereby authorized to charge the fees listed below to our Deposit Account No. 06-1135 under Order No. 7601/88086. The Director is also authorized to charge any fee deficiency with respect to this filing and any other fee required in connection with the present case, or credit any overpayment, to our Deposit Account No. 06-1135 under Order No. 7601/88086.

Fee Calculation

Applicant(s) calculate the filing fee as follows:

	Total		No. Extra	Rate	Fee
Basic National Stage Filing Fee					$ 300.00
National Stage Search Fee (Search Report prepared and provided to USPTO)					400.00
National Stage Examination Fee					200.00
Natl. Stage Application Size Fee				$ 250.00	
Claims in Excess of 20	7	20 =	0	$ 50.00	0.00
Independent Claims in Excess of 3	1	3 =	0	$ 200.00	0.00
Multiple Dependent Claims Fee				$ 360.00	360.00
TOTAL FEES DUE					$ 1,260.00

Correspondence in this case should be directed to Michael A. Sanzo at the address associated with Customer No.:

42798.

It is respectfully requested that the enclosed postpaid postcards be stamped with the serial number and the date the enclosed documents are received by the PTO and that they be returned as soon as possible.

Respectfully requested,

FITCH, EVEN, TABIN & FLANNERY

Michael A. Sanzo
Attorney for Applicants
Registration No. 36,912

MAS:ct
Enclosures

Application Data Sheet

Application Information

Application number::	
Filing date::	
Application type::	Regular
Subject Matter::	Utility
Suggested Classification::	
Suggested Group Art Unit::	
CD-Rom or CD-R?::	
Number of CD disks::	
Number of Copies of CDs::	
Sequence Submission?::	
Computer Readable Form (CRF)?::	
Number of Copies of CRF::	
Title::	Process for the Production of alpha-alkoxy/hydroxy-beta-(p-hydroxyphenyl) Propionic Acid Derivatives
Attorney Docket Number::	7601/88086
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	
Small Entity::	
Latin name::	
Variety denomination name::	
Petition Included?::	
Petition Type::	
Licensed US Govt. Agency::	
Contract or Grant Numbers::	
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type:: Inventor
Primary Citizenship Country:: Germany
Status:: Full capacity
Given Name:: Dieter
Family Name:: Most
City of Residence:: Bruchkobel
State or Province of mailing address::
Country of Residence:: Germany
Street of mailing address:: Fritz-Schubert-Ring 57
City of mailing address:: Bruchkobel
State or Province of mailing address::
Country of mailing address:: Germany
Postal or Zip Code of mailing address:: 63486
Applicant Authority Type:: Inventor
Primary Citizenship Country:: Slovakia
Status:: Full capacity
Given Name:: Pavol
Family Name:: Jakubec
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State or Province of mailing address::
Country of Residence:: Slovakia
Street of mailing address:: Kollarova 2454
City of mailing address:: Cadca
State or Province of mailing address::
Country of mailing address:: Slovakia
Postal or Zip Code of mailing address:: 02201
Applicant Authority Type:: Inventor
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Status:: Full capacity
Given Name:: Kai
Family Name:: Rossen
City of Residence:: Hanau
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Country of Residence:: Germany

Street of mailing address:: Handelstrasse 3B
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State or Province of mailing address::
Country of mailing address:: Germany
Postal or Zip Code of mailing address:: 63452

Correspondence Information

Correspondence Customer Number:: 42798

Representative Information

Representative Customer Number::	42798

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::

Foreign Priority Information

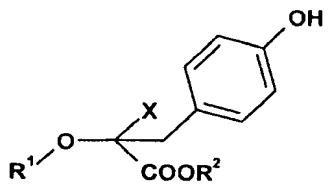
Country::	Application Number::	Filing Date::	Priority Claimed::
This Application U.S. National Stage of	PCT/EP2004/009621	August 28, 2004	Yes
Germany	103 43 097.0	September 18, 2003	Yes

Assignee Information

Assignee name:: Degussa AG
Street of mailing address:: Bennigsenplatz 1
City of mailing address:: Dusseldorf
State or Province of mailing address::
Country of mailing address:: Germany
Postal or Zip Code of mailing address:: DE-40474

Process for the Production of α-alkoxy/hydroxy-β-(p-hydroxyphenyl) Propionic Acid Derivatives

The present invention is directed at a process for the production of α-alkoxy/hydroxy-β-(p-hydroxyphenyl) propionic acid derivatives. In particular the invention concerns the production of compounds having the general formula (I)



(I)

Compounds having formula (I), in particular where X = H, are important intermediates for the production of biologically active compounds. For example, so-called peroxisome proliferator-activating receptor agonists (ragaglitazar) have a corresponding partial structure (J. Med. Chem. 2003, 46, 1306-17; Organic Process Research & Development 2003, 7, 82-88).

A number of syntheses have become known for the production of the compounds under consideration. For example, WO0140159 suggests inter alia a multistage synthesis route in which the corresponding condensation product is generated from the corresponding methoxybenzaldehyde and ethoxyacetic acid ester under basic conditions and the product thus obtained is eliminated to the conjugated system. Hydrogenation is followed by conversion to the corresponding acid, a classic resolution of racemates, elimination of the methyl protective group and finally another esterification. The total yield appears to be modest.

S. Ebdrup et al. propose a Wittig-Horner strategy starting

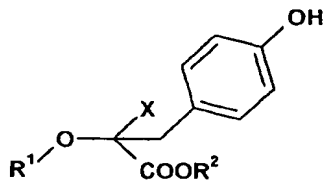
from 4-(benzyloxy)benzaldehyde and ethyl-2-(diethylphosphinyl)-2-ethoxyacetate.

In all cases production of the racemic compound requires a complex synthesis with many stages and expensive reagents before resolution into the enantiomers. As the costs and the environmental loading due to the resolution of the racemates, which occurs late on in the synthesis, require production of at least twice the amount of racemate, a simple and environmentally friendly synthesis of the compounds having formula (I) is important.

The object of the present invention was therefore to provide another production method for the compounds having the general formula (I). The method should be able to be used on an industrial scale very successfully from an economic and ecological perspective, i.e. it should be robust, start from as favourable starting materials as possible and involve few stages.

This and other objects not mentioned in any more detail but obviously arising from the prior art are achieved by a process with the features of the present claim 1. Preferred embodiments of the process according to the invention are described in the subordinate claims depending on claim 1.

In a process for the production of compounds having the general formula (I)



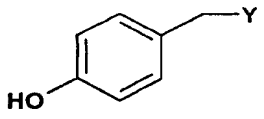
(I)

wherein

X = H or a group having an electron-attracting effect,

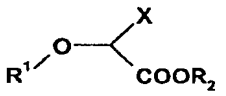
R^1 or R^2 are mutually independently H, (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_8) alkyl (C_3-C_8) cycloalkyl, (C_3-C_8)

cycloalkyl ((C_1-C_8) alkyl)$_{1-3}$, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_6-C_{18}) aryl, (C_7-C_{19}) aralkyl radical, (C_6-C_{18}) aryl ((C_1-C_8) alkyl)$_{1-3}$,
the stated object is achieved quite surprisingly, but no less successfully for that and especially advantageously according to the invention, by reacting compounds having the general formula (II)



(II)

wherein
Y represents a nucleofugal leaving group,
with compounds having the general formula (III)



(III)

wherein
R1, R2 and X can assume the meaning stated above,
under basic conditions.
Under the cited reaction conditions, compounds having formula (II) react so well with the nucleophile obtainable from (III) that the desired intermediates, such as e.g. α-alkoxy-β-(p-hydroxyphenyl) propionic acid can be obtained in up to a 90% yield. It is likely that the yield could be increased still further by additional process optimisation.
According to the invention this process is started from compounds that are available commercially.
For access to compounds having formula (III) by synthesis, reference is made to the following literature: Monatshefte Chemie 1965, 1677-1689; J. Chem. Soc., Perkin Trans. 1: Org. Bioorg. Chem. 1976, 23, 2483-4; Synthesis 1975, 4,

269-70; J. Chem. Soc,. 1933, 1628; Chem. Ber. 1991, 8, 1853-1863; JACS 1988, 110, 209-213.

In selecting groups X and Y, the person skilled in the art has a free choice in principle, provided that they are compatible with the reaction. Hydrogen and electron-attracting groups are suitable for X. The introduction of electron-attracting groups further increases the acidity of (III), which makes it possible to use milder bases. As groups X the person skilled in the art can preferably choose examples that afterwards allow a hydrogen radical to be introduced at the α-carbon atom as easily as possible. This can be done by a substitution or reduction reaction or elegantly also by a decarboxylation and/or decarbonylation reaction. In the latter context the use of corresponding 1,3-dicarboxyl or 1,3-dicarbonyl derivatives is particularly worthy of mention. It is therefore particularly preferred if X is a radical selected from the group containing CCl_3, CN, $COOR_1$, COR_1, $COCOOR_1$.
The radical Y is a nucleofugal leaving group. This type of radical is familiar to the person skilled in the art (Organikum, VEB Deutscher Verlag, 1986, 16th edition p. 170 ff). Mechanistic analyses suggest that the reaction proceeds via p-quinone methide. It is of course also conceivable, however, that the reaction proceeds in the manner of SN_1 via substitution of the benzyl cation or in the manner of SN_2 via a direct substitution of the leaving group Y. The mechanistic course of the reaction will be governed by the leaving group Y and the reaction conditions used. The use of radicals Y selected from the group containing OH, Cl, Br, OTs, OAc, $OCOCF_3$, OMs is conceivable.

With regard to the radicals R^1 and R^2 the person skilled in the art does not need to observe any restrictive boundary conditions. As stated, they should be inert in respect of the reaction and be as inexpensive as possible. In this context H or (C_1-C_8) alkyl are therefore preferred for both

radicals. Emphasis should be given to the use of the methyl or ethyl radical for R^1 and/or R^2.

The person skilled in the art also has a free choice of the solvent to be used. It should be as inexpensive as possible, again be inert under the reaction conditions and furthermore should allow the reaction to proceed in the best possible way. Organic solvents having a aprotic dipolar character are preferred, such as e.g. NMP, DMPU, DMF, DMSO, sulfolane. However, (C_1-C_8) alkyl alcohols can also be used for the reaction, such as e.g. tert.-amyl alcohol, ethanol, propanol, tert.-butanol, isopropanol, n- or sec-butanol. The use of polar aprotic solvents such as THF, MTBE, DME or CH_3CN or any mixtures of the cited solvents also seems conceivable.

The use of the base is governed by the nature of the deprotonating substrate (III) to be used. For example, for compounds (III) where X = H stronger bases such as LDA, NaH, KH, LiHMDS, KHMDS or NaHMDS must be used. As the electron-attracting effect of the radical X increases, the strength of the base to be used can be reduced more and more, so that (C_1-C_8) alkyl alkoxides (preferably dissolved or suspended in (C_1-C_8) alkyl alcohols) such as NaOMe, NaOEt, KOtBu etc., or stronger N bases such as Et_3N, DBU, DBN, TMG, pentamethyl guanidine, diisopropyl ethylamine, phosphazenes (R.Schwesinger, H.Schlemper, Angew.Chem.99, 1212 (1987); R.Schwesinger, Nachr. Chem. Tech. Lab. 38, 1214 (1990); H.Schlemper, University of Freiburg dissertation, 1990; R.Schwesinger, Chimia 39, 269 (1985); T.Pietzonka, D.Seebach, Chem. Ber. 124, 1837 (1990); H.-J.Gais, J.Vollhardt, .Krüger, Angew.Chem.100,1108 (1988); M.Fletschinger, B.Zipperer, H.Fritz, H.Prinzbach, Tetrahedron Lett. 28, 2517 (1987)) can be used for more CH-acid compounds (III).

The reaction is preferably performed by introducing the base into the respective solvent and adding the compound (III). The substrate (II) is then added to the

mixture and reacted at temperatures of -30°C to 120°C, preferably -20°C to 100°C, most particularly preferably -20°C to 80°C. The chosen sequence of addition can also be the other way round, however. The product is isolated by a method known to the person skilled in the art, e.g. after separating the salts by evaporating the filtrate in vacuo (-> ester) or after saponification, acidification preferably by crystallisation of the corresponding acid.

Further processing can then take place by methods familiar to the person skilled in the art (see p. 1, line 13).

Methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert.-butyl, pentyl, hexyl, heptyl or octyl together with all bonding isomers can be regarded as (C_1-C_8) alkyl.

(C_2-C_8) alkenyl is understood to be a (C_1-C_8) alkyl radical as set out above (with the exception of methyl), that displays at least a double bond.

(C_2-C_8) alkynyl is understood to be a (C_1-C_8) alkyl radical as set out above (with the exception of methyl), that displays at least a triple bond.

(C_3-C_8) cycloalkyl is understood to be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl radicals, etc. These can display radicals containing N or O atoms in the ring, such as e.g. 1-, 2-, 3-, 4-piperidyl, 1-, 2-, 3-pyrrolidinyl, 2-, 3-tetrahydrofuryl, 2-, 3-, 4-morpholinyl.

A (C_6-C_{18}) aryl radical is understood to be an aromatic radical having 6 to 18 C atoms. These include in particular compounds such as phenyl, naphthyl, anthryl, phenanthryl and biphenyl radicals.

A (C_7-C_{19}) aralkyl radical is a (C_6-C_{18}) aryl radical bonded to the molecule via a (C_1-C_8) alkyl radical.

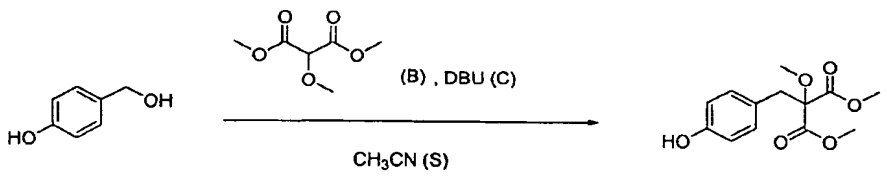
Within the meaning of the invention the term enantiomer-concentrated is understood to refer to the proportion of an enantiomer in the mixture with its optical antipode in a range between >50 % and <100 %.

The chiral structures shown refer to all possible diastereomers and enantiomers (R-, S-) as well as to mixtures thereof and the racemate.

The cited references are to be regarded as being included in the disclosure of this invention.

Examples:

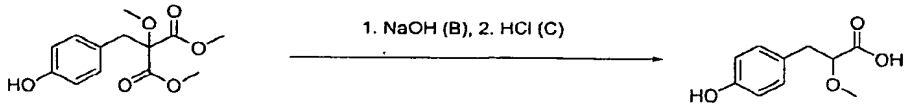
Example 1:



A

4-Hydroxybenzyl alcohol (1 g, 0.0081 mol, A) was suspended in acetonitrile (2 ml), to which 2-methoxydimethyl malonate (0.0161 mol, 2.61 g, 2.2 ml, B) and DBU (0.0041 mol, 0.62 g, 0.61 ml, C) were added. The suspension was refluxed for 3 hours. The reaction mixture was cooled and the solvent evaporated. 20 ml water were added to the residue and the emulsion obtained was extracted with 3 x 20 ml ethyl acetate. The collected organic phases were dried over MgSO4. After removal of the solvent by distillation a yellowish oil (1.92 g, 88 %) was obtained, which crystallised after being left to stand.

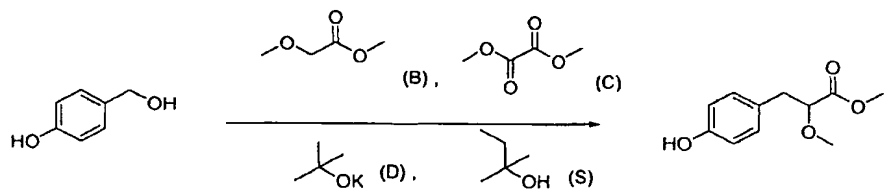
Example 2:



2-(4-Hydroxybenzyl)-2-methoxydimethyl malonate (1 g, 0.0037 mol) was added to a solution of NaOH (0.0112 mol, 0.45 g) in water (4 ml) and the reaction mixture was stirred for 3 hours at room temperature. 13 ml of concentrated HCl were then slowly added to the resulting solution and the emulsion was extracted with 3 x 10 ml ethyl acetate. The water phase was evaporated to dryness. The resulting white solid was dissolved in dilute HCl (5 ml

water and 1 ml concentrated HCl) and refluxed for 16 hours. After cooling, the solution was extracted with 3 x 10 ml methyl isobutyl ketone. The combined organic phases were dried over $MgSO_4$. After removal of the solvent by distillation an orange-coloured oil (0.5 g, 69 %) was obtained, which gradually crystallised after being left to stand.

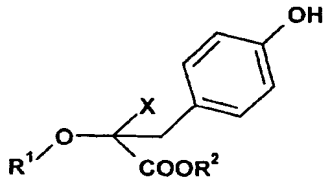
Example 3:



Potassium tert.-butylate (5.387 g, 0.0480 mol) was suspended in 2-methyl-2-butanol (30 ml). Then methoxymethyl acetate (0.0480 mol, 5.000 g, 4.8 ml) and dimethyl oxalate (0.0480 mol, 5.668 g) were added. The suspension was stirred for 1 hour at room temperature under an N_2 atmosphere. 4-Hydroxybenzyl alcohol (0.0408 mol, 5.065 g) was added in one portion and the reaction mixture refluxed for 30 minutes (oil bath 120 °C). The thick suspension was cooled in an ice bath to 5 °C. 100 ml MTBE were added. The insoluble solid was filtered off and the filter cake washed with 30 ml MTBE. The filtrate was concentrated to dry it and the residue dried to constant weight in an oil pump vacuum. After evaporation and drying, α-methoxy-β-(p-hydroxyphenyl) methyl propionate was obtained as an orange-coloured oil (8.0 g, 79 %). The methyl ester group was hydrolysed under the same conditions as in Example 2.

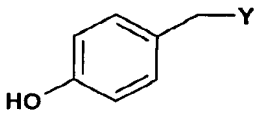
Claims:

1. Process for the production of compounds having the general formula (I)



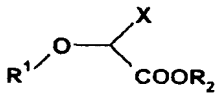
(I)

wherein
X is H or a group having an electron-attracting effect,
R^1 or R^2 are mutually independently H, (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_8) alkyl (C_3-C_8) cycloalkyl, (C_3-C_8) cycloalkyl $((C_1-C_8)$ alkyl$)_{1-3}$, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_6-C_{18}) aryl, (C_7-C_{19}) aralkyl radical, (C_6-C_{18}) aryl $((C_1-C_8)$ alkyl$)_{1-3}$,
by reacting compounds having the general formula (II)



(II)

wherein
Y represents a nucleofugal leaving group,
with compounds having the general formula (III)



(III)

wherein
R^1, R^2 and X can assume the meaning stated above,
under basic conditions.

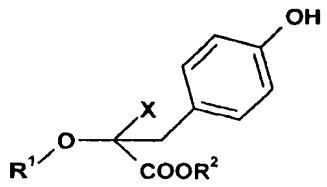
2. Process according to claim 1,
characterised in that
R^1 and/or R^2 is H or (C_1-C_8) alkyl,
Y is a radical selected from the group containing OH, Cl, Br, OTs, OAc, $OCOCF_3$, OMs,
X is a radical selected from the group containing H, CCl_3, CN, $COOR^1$, COR^1, $COCOOR^1$.

3. Process according to claim 1 and/or 2,
characterised in that
the reaction is performed in solvents selected from the group containing (C_1-C_8) alkyl alcohols, NMP, DMPU, DMF, DMSO, sulfolane, THF, MTBE, CH_3CN.

4. Process according to one or more of the preceding claims,
characterised in that
compounds selected from the group containing (C_1-C_8) alkyl alkoxides, Et_3N, DBU, DBN, TMG, pentamethyl guanidine, diisopropyl ethylamine, phosphazenes are used as base.

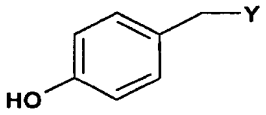
Abstract:

The present invention describes the production of compounds having the general formula (I)

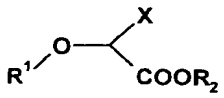


(I)

starting from compounds having the general formula (II) and (III)



(II)



(III)

The products are intermediates for the production of bioactive substances.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Most, *et al.*

U.S. Natl. Phase of: PCT/EP2004/009621

Intl. Filing Date: August 28, 2004

Filed: herewith

Appl. No: to be assigned

For: **Process for the Production of α-alkoxy/ hydroxy-β-(p-hydroxyphenyl) Propionic Acid Derivatives**

Art Unit: to be assigned

Examiner: to be assigned

Atty. Dkt.: 7601/88086

Preliminary Amendment

Commissioner of Patents
U.S. Patent and Trademark Office
Customer Window, **MS PCT**
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

In advance of prosecution, please amend the above-captioned application as described herein.

Amendments to the Specification begin on page 2 of the present document.

Remarks begin on page 3 of the present document.

Amendments to the Specification

On page 1 of the specification, after the title and before the text that presently begins on line 3, please add the following text:

> Cross Reference to Related Applications
>
> The present application represents U.S. national stage of international application PCT/EP2004/009621, which had an international filing date of August 28, 2004, and which was published in English under PCT Article 21(2) on March 24, 2005. The international application claims priority to German application 103 43 097.0, filed on September 18, 2003. These prior art applications are hereby incorporated by reference in their entirety.

Remarks

The present application represents U.S. national stage of international application PCT/EP2004/009621. The specification has been amended to cross-reference both the international application and a German application which the international application relied upon for priority. These amendments clearly do not add new matter to the application, and their entry is therefore respectfully requested.

Conclusion

In light of the amendments made herein, Applicants believe that the present application is now in condition for allowance. Early notice to this effect is earnestly solicited.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date March 15, 2006

1801 K Street, N.W., Suite 401L
Washington, DC 20006-1201
Telephone: (202) 419-7000

PCT REQUEST

Original (for **SUBMISSION**)

0	For receiving Office use only	
0-1	International Application No.	PCT/EP 2004 / 009621
0-2	International Filing Date	26 AUG 2004 (26.08.04)
0-3	Name of receiving Office and "PCT International Application"	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION

0-4	Form PCT/RO/101 PCT Request	
0-4-1	Prepared Using	PCT-SAFE [EASY mode] Version 3.50 (Build 0002.162)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	030285 OC
I	Title of Invention	PROCESS FOR THE PRODUCTION OF ALPHA-ALKOXY/HYDROXY-BETA-(P-HYDROXYPHENYL) PROPIONIC ACID DERIVATIVES
II	Applicant	
II-1	This person is	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	DEGUSSA AG
II-5	Address	Bennigsenplatz 1 40474 Düsseldorf Germany
II-6	State of nationality	DE
II-7	State of residence	DE
II-8	Telephone No.	0 61 81 / 59-39 24
II-9	Facsimile No.	0 61 81 / 59-43 04
III-1	Applicant and/or Inventor	
III-1-1	This person is	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	MOST, Dieter
III-1-5	Address	Fritz-Schubert-Ring 57 63486 Bruchköbel Germany
III-1-6	State of nationality	DE
III-1-7	State of residence	DE

PCT REQUEST

Original (for **SUBMISSION**)

III-2	**Applicant and/or inventor**	
III-2-1	This person is	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	JAKUBEC, Pavol
III-2-5	Address	Kollarova 2454 02201 Cadca Slovakia
III-2-6	State of nationality	SK
III-2-7	State of residence	SK
III-3	**Applicant and/or inventor**	
III-3-1	This person is	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	ROSSEN, Kai
III-3-5	Address	Händelstrasse 3B 63452 Hanau Germany
III-3-6	State of nationality	DE
III-3-7	State of residence	DE
IV-1	**Agent or common representative; or address for correspondence** The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	common representative
IV-1-1	Name	DEGUSSA AG
IV-1-2	Address	Intellectual Property Management PATENTE und MARKEN Standort Hanau Postfach 13 45 63403 Hanau Germany
IV-1-3	Telephone No.	0 61 81 / 59-39 24
IV-1-4	Facsimile No.	0 61 81 / 59-43 04

PCT REQUEST

Original (for **SUBMISSION**)

V	DESIGNATIONS		
V-1	The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.		
V-2	Item V-2 may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. As to the consequences of such national law provisions in these and certain other States, see Designations in PCT-SAFE Help.	DE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	18 September 2003 (18.09.2003)	
VI-1-2	Number	103 43 097.0	
VI-1-3	Country	DE	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	4	✓
IX-2	Description	9	-
IX-3	Claims	2	-
IX-4	Abstract	1	✓
IX-5	Drawings	0	-
IX-7	TOTAL	16	

030285 OC

PCT REQUEST

Original (for **SUBMISSION**)

	Accompanying Items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	reference no. AV 43529	-
IX-17	PCT-SAFE physical media	-	✓
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative		
X-1-1	Name	DEGUSSA AG	
X-1-2	Name of signatory	i. V. Dr. Stefan Retzow	
X-1-3	Capacity	AV 43529	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	28.08.04	28 AUG 2004
10-2	Drawings:		
10-2-1	Received		
10-2-2	Not received		
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application		
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)		
10-5	International Searching Authority	ISA/EP	
10-6	Transmittal of search copy delayed until search fee is paid		

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT

Original (for SUBMISSION)

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to international application PCT/EP2004/009621 (if furnishing declaration pursuant to Rule 26ter). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name (LAST, First)	MOST, Dieter
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Bruchköbel, Germany
VIII-4-1-1-3	Mailing address:	Fritz-Schubert-Ring 57 D-63486 Bruchköbel Germany
VIII-4-1-1-4	Citizenship:	DE
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	Dieter Most
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	21.09.04

PCT

Original (for SUBMISSION)

VIII-4-1-2-1	Name (LAST, First)	JAKUBEC, Pavol
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Cadca, Slovakia
VIII-4-1-2-3	Mailing address:	Kollarova 2454 02201 Cadca Slovakia
VIII-4-1-2-4	Citizenship:	SK
VIII-4-1-2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-2-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	
VIII-4-1-3-1	Name (LAST, First)	ROSSEN, Kai
VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	Hanau, Germany
VIII-4-1-3-3	Mailing address:	Händelstrasse 3B D-63452 Hanau Germany
VIII-4-1-3-4	Citizenship:	DE
VIII-4-1-3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	Sept. 24 2004

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to international application PCT/ EP2004/009621 (if furnishing declaration pursuant to Rule 26ter). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name (LAST, First)	MOST, Dieter
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Bruchköbel, Germany
VIII-4-1-1-3	Mailing address:	Fritz-Schubert-Ring 57 D-63486 Bruchköbel Germany
VIII-4-1-1-4	Citizenship:	DE
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

PCT

Original (for SUBMISSION)

VIII-4-1-2-1	Name (LAST, First)	JAKUBEC, Pavol
VIII-4-1-2-2	Residence: (city and either US State, if applicable, or country)	Cadca, Slovakia
VIII-4-1-2-3	Mailing address:	Kollarova 2454 02201 Cadca Slovakia
VIII-4-1-2-4	Citizenship:	SK
VIII-4-1-2-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	Jakubec Pavol
VIII-4-1-2-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	10. 9. 2004
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VIII-4-1-3-2	Residence: (city and either US State, if applicable, or country)	Hanau, Germany
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VIII-4-1-3-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-3-6	Date (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

030285 OC

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 March 2005 (24.03.2005)

PCT

(10) International Publication Number
WO 2005/026096 A2

(51) International Patent Classification[7]: C07C 67/00

(21) International Application Number:
PCT/EP2004/009621

(22) International Filing Date: 28 August 2004 (28.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
103 43 097.0 18 September 2003 (18.09.2003) DE

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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Published:
— *without international search report and to be republished upon receipt of that report*

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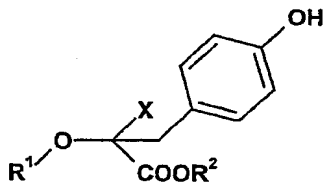
(54) Title: PROCESS FOR THE PRODUCTION OF ALPHA-ALKOXY/HYDROXY-BETA-(P-HYDROXYPHENYL) PROPIONIC ACID DERIVATIVES

(57) Abstract: The present invention describes the production of compounds having the general formula (I) starting from compounds having the general formula (II) and (III) The products are intermediates for the production of bioactive substances.

WO 2005/026096 A2

Process for the production of α-alkoxy/hydroxy-β-(p-hydroxyphenyl) propionic acid derivatives

The present invention is directed at a process for the production of α-alkoxy/hydroxy-β-(p-hydroxyphenyl) propionic acid derivatives. In particular the invention concerns the production of compounds having the general formula (I)



(I)

Compounds having formula (I), in particular where X = H, are important intermediates for the production of biologically active compounds. For example, so-called peroxisome proliferator-activating receptor agonists (ragaglitazar) have a corresponding partial structure (J. Med. Chem. 2003, 46, 1306-17; Organic Process Research & Development 2003, 7, 82-88).

A number of syntheses have become known for the production of the compounds under consideration. For example, WO0140159 suggests inter alia a multistage synthesis route in which the corresponding condensation product is generated from the corresponding methoxybenzaldehyde and ethoxyacetic acid ester under basic conditions and the product thus obtained is eliminated to the conjugated system. Hydrogenation is followed by conversion to the corresponding acid, a classic resolution of racemates, elimination of the methyl protective group and finally another esterification. The total yield appears to be modest.

S. Ebdrup et al. propose a Wittig-Horner strategy starting

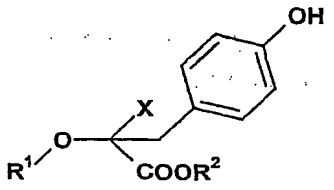
from 4-(benzyloxy)benzaldehyde and ethyl-2-(diethylphosphinyl)-2-ethoxyacetate.

In all cases production of the racemic compound requires a complex synthesis with many stages and expensive reagents before resolution into the enantiomers. As the costs and the environmental loading due to the resolution of the racemates, which occurs late on in the synthesis, require production of at least twice the amount of racemate, a simple and environmentally friendly synthesis of the compounds having formula (I) is important.

The object of the present invention was therefore to provide another production method for the compounds having the general formula (I). The method should be able to be used on an industrial scale very successfully from an economic and ecological perspective, i.e. it should be robust, start from as favourable starting materials as possible and involve few stages.

This and other objects not mentioned in any more detail but obviously arising from the prior art are achieved by a process with the features of the present claim 1. Preferred embodiments of the process according to the invention are described in the subordinate claims depending on claim 1.

In a process for the production of compounds having the general formula (I)



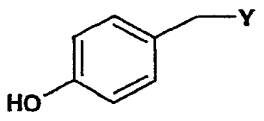
(I)

wherein

X = H or a group having an electron-attracting effect,

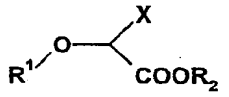
R^1 or R^2 are mutually independently H, (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_8) alkyl (C_3-C_8) cycloalkyl, (C_3-C_8)

cycloalkyl ((C_1-C_8) alkyl)$_{1-3}$, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_6-C_{18}) aryl, (C_7-C_{19}) aralkyl radical, (C_6-C_{18}) aryl ((C_1-C_8) alkyl)$_{1-3}$,
the stated object is achieved quite surprisingly, but no less successfully for that and especially advantageously according to the invention, by reacting compounds having the general formula (II)



(II)

wherein
Y represents a nucleofugal leaving group,
with compounds having the general formula (III)



(III)

wherein
R1, R2 and X can assume the meaning stated above,
under basic conditions.
Under the cited reaction conditions, compounds having formula (II) react so well with the nucleophile obtainable from (III) that the desired intermediates, such as e.g. α-alkoxy-β-(p-hydroxyphenyl) propionic acid can be obtained in up to a 90% yield. It is likely that the yield could be increased still further by additional process optimisation.
According to the invention this process is started from compounds that are available commercially.
For access to compounds having formula (III) by synthesis, reference is made to the following literature: Monatshefte Chemie 1965, 1677-1689; J. Chem. Soc., Perkin Trans. 1: Org. Bioorg. Chem. 1976, 23, 2483-4; Synthesis 1975, 4,

269-70; J. Chem. Soc,. 1933, 1628; Chem. Ber. 1991, 8, 1853-1863; JACS 1988, 110, 209-213.

In selecting groups X and Y, the person skilled in the art has a free choice in principle, provided that they are compatible with the reaction. Hydrogen and electron-attracting groups are suitable for X. The introduction of electron-attracting groups further increases the acidity of (III), which makes it possible to use milder bases. As groups X the person skilled in the art can preferably choose examples that afterwards allow a hydrogen radical to be introduced at the α-carbon atom as easily as possible. This can be done by a substitution or reduction reaction or elegantly also by a decarboxylation and/or decarbonylation reaction. In the latter context the use of corresponding 1,3-dicarboxyl or 1,3-dicarbonyl derivatives is particularly worthy of mention. It is therefore particularly preferred if X is a radical selected from the group containing CCl_3, CN, $COOR_1$, COR_1, $COCOOR_1$.
The radical Y is a nucleofugal leaving group. This type of radical is familiar to the person skilled in the art (Organikum, VEB Deutscher Verlag, 1986, 16th edition p. 170 ff). Mechanistic analyses suggest that the reaction proceeds via p-quinone methide. It is of course also conceivable, however, that the reaction proceeds in the manner of SN_1 via substitution of the benzyl cation or in the manner of SN_2 via a direct substitution of the leaving group Y. The mechanistic course of the reaction will be governed by the leaving group Y and the reaction conditions used. The use of radicals Y selected from the group containing OH, Cl, Br, OTs, OAc, $OCOCF_3$, OMs is conceivable.

With regard to the radicals R^1 and R^2 the person skilled in the art does not need to observe any restrictive boundary conditions. As stated, they should be inert in respect of the reaction and be as inexpensive as possible. In this context H or (C_1-C_8) alkyl are therefore preferred for both

radicals. Emphasis should be given to the use of the methyl or ethyl radical for R^1 and/or R^2.

The person skilled in the art also has a free choice of the solvent to be used. It should be as inexpensive as possible, again be inert under the reaction conditions and furthermore should allow the reaction to proceed in the best possible way. Organic solvents having a aprotic dipolar character are preferred, such as e.g. NMP, DMPU, DMF, DMSO, sulfolane. However, (C_1-C_8) alkyl alcohols can also be used for the reaction, such as e.g. tert.-amyl alcohol, ethanol, propanol, tert.-butanol, isopropanol, n- or sec-butanol. The use of polar aprotic solvents such as THF, MTBE, DME or CH_3CN or any mixtures of the cited solvents also seems conceivable.

The use of the base is governed by the nature of the deprotonating substrate (III) to be used. For example, for compounds (III) where X = H stronger bases such as LDA, NaH, KH, LiHMDS, KHMDS or NaHMDS must be used. As the electron-attracting effect of the radical X increases, the strength of the base to be used can be reduced more and more, so that (C_1-C_8) alkyl alkoxides (preferably dissolved or suspended in (C_1-C_8) alkyl alcohols) such as NaOMe, NaOEt, KOtBu etc., or stronger N bases such as Et_3N, DBU, DBN, TMG, pentamethyl guanidine, diisopropyl ethylamine, phosphazenes (R.Schwesinger, H.Schlemper, Angew.Chem.99, 1212 (1987); R.Schwesinger, Nachr. Chem. Tech. Lab. 38, 1214 (1990); H.Schlemper, University of Freiburg dissertation, 1990; R.Schwesinger, Chimia 39, 269 (1985); T.Pietzonka, D.Seebach, Chem. Ber. 124, 1837 (1990); H.-J.Gais, J.Vollhardt, .Krüger, Angew.Chem.100,1108 (1988); M.Fletschinger, B.Zipperer, H.Fritz, H.Prinzbach, Tetrahedron Lett. 28, 2517 (1987)) can be used for more CH-acid compounds (III).

The reaction is preferably performed by introducing the base into the respective solvent and adding the compound (III). The substrate (II) is then added to the

mixture and reacted at temperatures of -30°C to 120°C, preferably -20°C to 100°C, most particularly preferably -20°C to 80°C. The chosen sequence of addition can also be the other way round, however. The product is isolated by a method known to the person skilled in the art, e.g. after separating the salts by evaporating the filtrate in vacuo (-> ester) or after saponification, acidification preferably by crystallisation of the corresponding acid.

Further processing can then take place by methods familiar to the person skilled in the art (see p. 1, line 13).

Methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert.-butyl, pentyl, hexyl, heptyl or octyl together with all bonding isomers can be regarded as (C_1-C_8) alkyl.

(C_2-C_8) alkenyl is understood to be a (C_1-C_8) alkyl radical as set out above (with the exception of methyl), that displays at least a double bond.

(C_2-C_8) alkynyl is understood to be a (C_1-C_8) alkyl radical as set out above (with the exception of methyl), that displays at least a triple bond.

(C_3-C_8) cycloalkyl is understood to be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl radicals, etc. These can display radicals containing N or O atoms in the ring, such as e.g. 1-, 2-, 3-, 4-piperidyl, 1-, 2-, 3-pyrrolidinyl, 2-, 3-tetrahydrofuryl, 2-, 3-, 4-morpholinyl.

A (C_6-C_{18}) aryl radical is understood to be an aromatic radical having 6 to 18 C atoms. These include in particular compounds such as phenyl, naphthyl, anthryl, phenanthryl and biphenyl radicals.

A (C_7-C_{19}) aralkyl radical is a (C_6-C_{18}) aryl radical bonded to the molecule via a (C_1-C_8) alkyl radical.

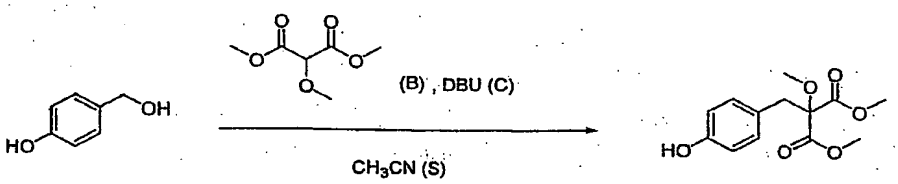
Within the meaning of the invention the term enantiomer-concentrated is understood to refer to the proportion of an enantiomer in the mixture with its optical antipode in a range between >50 % and <100 %.

The chiral structures shown refer to all possible diastereomers and enantiomers (R-, S-) as well as to mixtures thereof and the racemate.

The cited references are to be regarded as being included in the disclosure of this invention.

Examples:

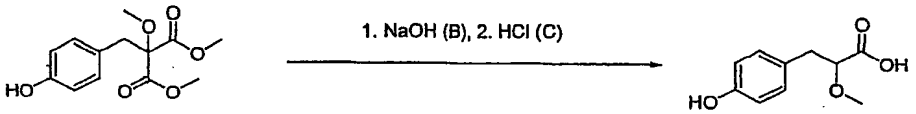
Example 1:



A

4-Hydroxybenzyl alcohol (1 g, 0.0081 mol, A) was suspended in acetonitrile (2 ml), to which 2-methoxydimethyl malonate (0.0161 mol, 2.61 g, 2.2 ml, B) and DBU (0.0041 mol, 0.62 g, 0.61 ml, C) were added. The suspension was refluxed for 3 hours. The reaction mixture was cooled and the solvent evaporated. 20 ml water were added to the residue and the emulsion obtained was extracted with 3 x 20 ml ethyl acetate. The collected organic phases were dried over MgSO4. After removal of the solvent by distillation a yellowish oil (1.92 g, 88 %) was obtained, which crystallised after being left to stand.

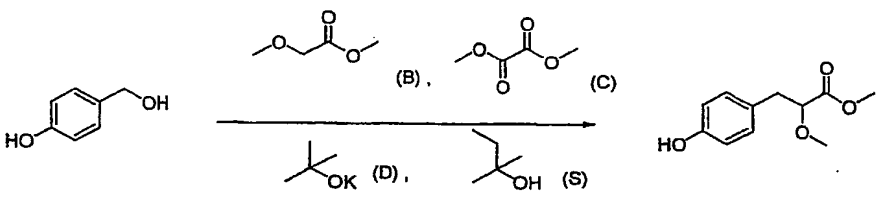
Example 2:



2-(4-Hydroxybenzyl)-2-methoxydimethyl malonate (1 g, 0.0037 mol) was added to a solution of NaOH (0.0112 mol, 0.45 g) in water (4 ml) and the reaction mixture was stirred for 3 hours at room temperature. 13 ml of concentrated HCl were then slowly added to the resulting solution and the emulsion was extracted with 3 x 10 ml ethyl acetate. The water phase was evaporated to dryness. The resulting white solid was dissolved in dilute HCl (5 ml

water and 1 ml concentrated HCl) and refluxed for 16 hours. After cooling, the solution was extracted with 3 x 10 ml methyl isobutyl ketone. The combined organic phases were dried over $MgSO_4$. After removal of the solvent by distillation an orange-coloured oil (0.5 g, 69 %) was obtained, which gradually crystallised after being left to stand.

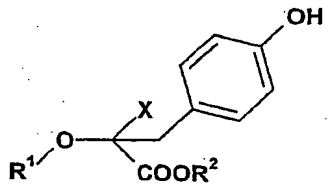
Example 3:



Potassium tert.-butylate (5.387 g, 0.0480 mol) was suspended in 2-methyl-2-butanol (30 ml). Then methoxymethyl acetate (0.0480 mol, 5.000 g, 4.8 ml) and dimethyl oxalate (0.0480 mol, 5.668 g) were added. The suspension was stirred for 1 hour at room temperature under an N_2 atmosphere. 4-Hydroxybenzyl alcohol (0.0408 mol, 5.065 g) was added in one portion and the reaction mixture refluxed for 30 minutes (oil bath 120 °C). The thick suspension was cooled in an ice bath to 5 °C. 100 ml MTBE were added. The insoluble solid was filtered off and the filter cake washed with 30 ml MTBE. The filtrate was concentrated to dry it and the residue dried to constant weight in an oil pump vacuum. After evaporation and drying, α-methoxy-β-(p-hydroxyphenyl) methyl propionate was obtained as an orange-coloured oil (8.0 g, 79 %). The methyl ester group was hydrolysed under the same conditions as in Example 2.

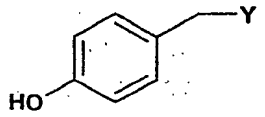
Claims:

1. Process for the production of compounds having the general formula (I)



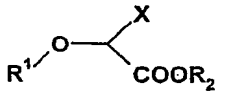
(I)

wherein
X is H or a group having an electron-attracting effect,
R^1 or R^2 are mutually independently H, (C_1-C_8) alkyl, (C_3-C_8) cycloalkyl, (C_1-C_8) alkyl (C_3-C_8) cycloalkyl, (C_3-C_8) cycloalkyl ((C_1-C_8) alkyl)$_{1-3}$, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_6-C_{18}) aryl, (C_7-C_{19}) aralkyl radical, (C_6-C_{18}) aryl ((C_1-C_8) alkyl)$_{1-3}$,
by reacting compounds having the general formula (II)



(II)

wherein
Y represents a nucleofugal leaving group,
with compounds having the general formula (III)



(III)

wherein
R^1, R^2 and X can assume the meaning stated above,
under basic conditions.

2. Process according to claim 1,
characterised in that
R^1 and/or R^2 is H or (C_1-C_8) alkyl,
Y is a radical selected from the group containing OH, Cl, Br, OTs, OAc, $OCOCF_3$, OMs,
X is a radical selected from the group containing H, CCl_3, CN, $COOR^1$, COR^1, $COCOOR^1$.

3. Process according to claim 1 and/or 2,
characterised in that
the reaction is performed in solvents selected from the group containing (C_1-C_8) alkyl alcohols, NMP, DMPU, DMF, DMSO, sulfolane, THF, MTBE, CH_3CN.

4. Process according to one or more of the preceding claims,
characterised in that
compounds selected from the group containing (C_1-C_8) alkyl alkoxides, Et_3N, DBU, DBN, TMG, pentamethyl guanidine, diisopropyl ethylamine, phosphazenes are used as base.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 March 2005 (24.03.2005)

PCT

(10) International Publication Number
WO 2005/026096 A3

(51) International Patent Classification[7]: C07C 67/343, 69/734, 51/353, 59/64

(21) International Application Number: PCT/EP2004/009621

(22) International Filing Date: 28 August 2004 (28.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
103 43 097.0 18 September 2003 (18.09.2003) DE

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Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
12 May 2005

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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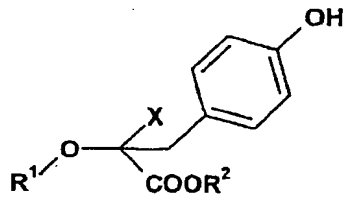
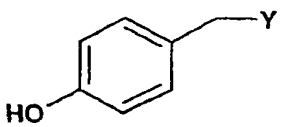
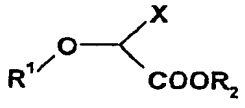


(I)



(II)



(III)

(57) Abstract: The present invention describes the production of compounds having the general formula (I) starting from compounds having the general formula (II) and (III) The products are intermediates for the production of bioactive substances.

WO 2005/026096 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/009621

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C67/343 C07C69/734 C07C51/353 C07C59/64

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	REINHARD SARGES ET AL: "Glucose transport-enhancing and hypoglycemic activity of 2-methyl-2-phenoxy-3-phenylpropanoic acids" JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, 1996, pages 4783-4803, XP002319864 page 4784: Scheme 1, "General method A" and Scheme 3, "General Method C"; page 4787: Table I	1-4

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 March 2005	17/03/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Sen, A

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/009621

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ERICH GRAF VON ROEDERN ET AL: "Bis-substituted malonic acid hydroxamate derivatives as Inhibitors of human neutrophil collagenase (MMP8)" JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, no. 16, 1998, pages 3041-3047, XP002319763 page 3042, Scheme 1; Table 1, in particular compound 19	1-4
Y	US 4 081 475 A (SPIVACK ET AL) 28 March 1978 (1978-03-28) column 2, lines 20-35 and 40-54; column 2, lines 60-69; Examples	1-4
Y	US 3 721 704 A (DEXTER M,US) 20 March 1973 (1973-03-20) column 4, lines 15-68; column 5, lines 15-29; Examples 1-4	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/009621

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4081475 A	28-03-1978	NONE	
US 3721704 A	20-03-1973	AT 281429 B	25-05-1970
		BE 710873 A	16-08-1968
		CH 496762 A	30-09-1970
		DE 1668916 A1	13-04-1972
		DE 1793708 A1	11-01-1973
		ES 350929 A1	16-05-1969
		FR 1564677 A	17-03-1969
		GB 1226371 A	24-03-1971
		NL 6802255 A ,B	19-08-1968
		NL 7401565 A	25-04-1974
		NL 7401568 A ,B	25-04-1974
		US 3907862 A	23-09-1975

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/009621	28.08.2004	18.09.2003

International Patent Classification (IPC) or both national classification and IPC
C07C67/343, C07C69/734, C07C51/353, C07C59/64

Applicant
DEGUSSA AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Sen, A

Telephone No. +49 89 2399-8328

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

D1: JOURNAL OF MEDICINAL CHEMISTRY, vol. 39, 1996, pages 4783 - 4803
D2: JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, 1998, pages 3041-3047
D3: US-A-4 081 475
D4: US-A-3 721 704

SECTION V:
Novelty - The subject-matter of claim 1 meets the requirements of Article 33(2) PCT since the cited prior art does not describe specifically the production of α-alkoxy / hydroxy - β-(p-hydroxyphenyl)- propionic acid derivatives of general formula (I) by the alkylation reaction of α-alkoxy / α-phenoxy or simply hydroxy- substituted acetic esters with p-hydroxybenzyl derivatives.

Inventive step - The set of claims on file meets an objection of lack of inventive step under Article 33(3) PCT as a surprising/ unexpected effect for the subject-matter claimed is not evident.
There are indeed clear indications in the prior art connecting the preparation of the compounds similar to the present compounds of general formula (I) by **the alkylation reaction of a reactive substituted benzyl derivative** (see D1: page 4784, Scheme 1 / Scheme 3: "benzyl halides"; see D2: page 3042: Scheme 1 and Table 1, $PhCH_2$-X, whereby X is halide, e.g., Br; see D3: column 2, lines 55-70, 4-hydroxybenzyl bromide / chloride; see D4: column 4, lines 30-40, substituted 4-hydroxybenzyl chloride) **with a compound of general formula R_1-O-CHX-$COOR_2$** (see D1: page 4784, Scheme 1 / Scheme 3; page 4787, Table 1; see also pages 4794 and 4795 **"General Method A"** and page 4796 **"General Method C"**; see D2: page 3042: **Scheme 1, first equation** and Table 1 for the definitions, in particular see the definitions for compound 19; see D3: **column 2, lines 20-35** and 40-54; column 2, lines 60-69; Examples; see D4: **column 4, lines 15-68**; **column 5, lines 15-29**; Examples 1-4). Differences between the present application and the documents described in the art relate to details in the structure of the reagents. These details, e.g. the presence / absence of an hydroxy group on the phenyl ring of the benzyl halide reagent, the substitution of the acetic ester, however, do the influence at all the chemistry involved in the alkylation of, for example, a malonate type compound at the C2 position with an alkyl halide in the presence of a base.

SECTION VIII:

A problem of lack of clarity within the meaning of Article 6 PCT is present with regard to the present application, in particular with regard to the following expressions used in claim 1: "X is a group having an electron-attracting effect", "Y represents a nucleofugal leaving group" and "R^1, R^2 and X can assume the meaning stated above". These expressions are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear.

The final compound obtained in Example 3 appears incorrect in view of the presence of the reagent (C).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Most, *et al.*

U.S. Natl. Phase of: PCT/EP2004/009621

Intl. Filing Date: August 28, 2004

Filed: herewith

Appl. No.: to be assigned

For: **Process for the Production of α-alkoxy/ hydroxy-β-(p-hydroxyphenyl) Propionic Acid Derivatives**

Art Unit: to be assigned

Examiner: to be assigned

Atty. Dkt.: 7601/88086

General Authorization for Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(3)

Commissioner of Patents
U.S. Patent and Trademark Office
Customer Service Window, **MS PCT**
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

Applicants hereby request under 37 C.F.R. §1.136(a)(3) by this general authorization that any concurrent or future reply submitted by Applicants to the United States Patent and Trademark Office for the above-identified patent application requiring a petition for an extension of time under §1.136(a) for its timely submission be treated as incorporating therein a petition for an extension of time for the appropriate length of time.

If Applicants do not timely pay for any extension fee(s) pursuant to 37 C.F.R. §1.136(a) which may become due for this application under 37 C.F.R. §1.17 by check, the Director is hereby authorized to charge such fee(s), and any additional fees which may be required in this application under 37 C.F.R. §§1.16-1.17 during its entire pendency, or credit any overpayment, to Deposit Account No. 06-1135 under Order No. 7601/88086.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date March 15, 2006
1801 K Street, N.W., Suite 401L
Washington, DC 20006-1201
Phone: (202) 419-7013

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of:

Most, *et al.*

U.S. Natl. Phase of: PCT/EP2004/009621

Intl. Filing Date: August 28, 2004

Filed: herewith

Appl. No.: to be assigned

For: **Process for the Production of α-alkoxy/ hydroxy-β-(p-hydroxyphenyl) Propionic Acid Derivatives**

Art Unit: to be assigned

Examiner: to be assigned

Atty. Dkt.: 7601/88086

General Authorization to Charge Deposit Account

Commissioner of Patents
U.S. Patent and Trademark Office
Customer Service Window, **MS PCT**
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

The Director is hereby authorized to charge any additional fees which may be required in this application under 37 C.F.R. §§1.16-1.17 during its entire pendency, or credit any overpayment, to Deposit Account No. 06-1135 under Order No. 7601/88086.

Respectfully submitted,

FITCH, EVEN, TABIN & FLANNERY

By Michael A. Sanzo

Michael A. Sanzo
Reg. No. 36,912
Attorney for Applicants

Date March 15, 2006
1801 K Street, N.W., Suite 401L
Washington, DC 20006-1201
Phone: (202) 419-7013

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

DEGUSSA AG
Intellectual Property Management
Patente und Marken
Standort Hanau
Postfach 13 45
63403 Hanau
Germany

Date of mailing (day/month/year) 22 November 2004 (22.11.2004)	
Applicant's or agent's file reference 030285 OC	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2004/009621	International filing date (day/month/year) 28 August 2004 (28.08.2004)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 18 September 2003 (18.09.2003)
Applicant DEGUSSA AG et al	

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. (If applicable) The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a) , the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. (If applicable) An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
18 Sept 2003 (18.09.2003)	103 43 097.0	DE	12 Octo 2004 (12.10.2004)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.89.75

Authorized officer
Mathieu BLANC (Fax 338 89 75)

Telephone No. (41-22) 338 9986

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

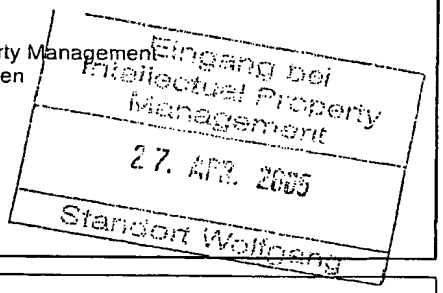
PCT

FIRST NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH DO NOT APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

DEGUSSA AG
Intellectual Property Management
Patente und Marken
Standort Hanau
Postfach 13 45
63403 Hanau
ALLEMAGNE



Date of mailing *(day/month/year)*	
21 April 2005 (21.04.2005)	
Applicant's or agent's file reference 030285 OC	**IMPORTANT NOTICE**
International application No. PCT/EP2004/009621	International filing date *(day/month/year)* 28 August 2004 (28.08.2004)
Priority date *(day/month/year)* 18 September 2003 (18.09.2003)	
Applicant DEGUSSA AG et al	

1. **ATTENTION**: For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), **does apply**, please see Form PCT/IB/308(Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below:
24 March 2005 (24.03.2005)

   CH

   In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, **does not apply**, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1 :

   LU, SE, TZ, UG, ZM

   In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

   For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of **19 months** from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, **subject to what is said in the following paragraph**, be **20 MONTHS** from the priority date.

   In practice, **time limits other than the 20-month time limit** will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For **regular updates on the applicable time limits** (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

   It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Ellen Moyse
Facsimile No.+41 22 740 14 35	Facsimile No.+41 22 338 89 75

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

To:
DEGUSSA AG
Intellectual Property Management
Patente und Marken
Standort Hanau
Postfach 13 45
63403 Hanau
ALLEMAGNE

NOTIFICATION RELATING TO
DECLARATION MADE UNDER PCT RULE 4.17

(PCT Rules 26*ter*.2(b), 47.1(a-*ter*) and 48.2(a)(x)
and Administrative Instructions, Section 419)

Date of mailing (*day/month/year*) 22 November 2004 (22.11.2004)	
Applicant's or agent's file reference 030285 OC	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2004/009621	International filing date (*day/month/year*) 28 August 2004 (28.08.2004)
Applicant DEGUSSA AG	

1. The applicant is hereby **notified** of the following regarding the declaration indicated below in respect of (*name(s) indicated in the declaration*) _____:

   (i) ☐ declaration as to the identity of the inventor (Rules 4.17(i) and 51*bis*.1(a)(i) and Section 211)

   (ii) ☐ declaration as to the applicant's entitlement, as at the international filing date, to apply for or be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii) and Section 212)

   (iii) ☐ declaration as to the applicant's entitlement, as at the international filing date, to claim priority of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii) and Section 213)

   (iv) ☒ declaration of inventorship (for the purposes of the designation of the United States of America) (Rules 4.17(iv) and 51*bis*.1(a)(iv) and Section 214)

   (v) ☐ declaration as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51*bis*.1(a)(v) and Section 215)

2. ☒ **Addition or correction of the declaration within the time limit under Rule 26*ter*.1.**

   The added or corrected declaration was received on *(date)*, 25 October 2004, (25.10.2004), which was received within the time limit under Rule *26ter*.1.

   Any declaration referred to under items 1(i) to (iv) whether or not the declaration complies with Rule 4.17, will be communicated to the designated Offices concerned pursuant to Rule 47.1(a-*ter*) and any declaration referred to under item 1(v) will be published as part of the pamphlet pursuant to Rule 48.2(a)(x).

3. ☐ **Failure to add or correct the declaration within the time limit under Rule 26*ter*.1.**

   The declaration, was received on *(date)*_____, which was **after** the expiration of the time limit under Rule 26*ter*.1; therefore, any such declaration referred to under items 1(i) to (iv) will **not** be communicated to the designated Offices concerned, any such declaration referred to under item 1(v) will **not** be published as part of the pamphlet, and any signed declaration referred to under item 1(iv) is attached. **Such declaration should be submitted by the applicant directly to the designated Offices concerned.**

4. The applicant's attention is drawn to Rule 51*bis*.2 which provides that the designated Office shall not, unless it may reasonably doubt the veracity of the declaration concerned, require any document or evidence relating to the subject matter of any declaration complying with Rule 4.17(i) to (iv) which is contained in the request or submitted to the International Bureau or directly to the designated Office. Note, however, that Rule 51*bis*.2 may not apply in respect of certain States. For further information, see Notes to the request form, Box No. VIII.

5. A copy of this notification is being sent to the receiving Office and the International Searching Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Mathieu BLANC (Fax 338 89 75)
Facsimile No. (41-22) 338.89.75	Telephone No. (41-22) 338.99.86

Form PCT/IB/371 (March 2001)

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EP-13F February 2002